CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM 8 CHEMICALS IDENTIFIED BY US EPA

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Reproductive and Cancer Hazard Assessment Section
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The 8 chemicals listed in the table below may meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

US EPA has been identified as an authoritative body for purposes of Proposition 65 (22 CCR Section 12306(l)) and has identified the chemicals in the table below as causing developmental or reproductive toxicity (DART). This was done by that Agency in implementing its Toxics Release Inventory (TRI) program (*i.e.*, Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 [EPCRA]). On the basis of identifying chemicals that caused reproductive, developmental and/or other toxicities the US EPA added a number of chemicals to the TRI list. The US EPA published its toxicity findings in the *Federal Register* (**59:**1788-1859, 1994 and **59:**61432-61485, 1994). In proposing specific chemicals for addition to the TRI list, the Agency stated that a hazard assessment was performed for each candidate, "…in accordance with relevant EPA guidelines for each adverse human health or environmental effect…" (*Federal Register* **59:**1790).

OEHHA has found that the chemicals in the table below have been "formally identified" as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306[d]) because the chemicals have "been identified as causing … reproductive toxicity by the authoritative body" (*i.e.*, US EPA) "in a document that indicates that such identification is a final action" (*e.g.*, the TRI *Final Rule* [*Federal Register* **59:**61432]) and have "been included on a list of chemicals causing … reproductive toxicity issued by the authoritative body" "and the document specifically and accurately identifies the chemical" and has been "published by the authoritative body in a publication, such as, but not limited to the federal register…"

OEHHA also finds that the criteria for "as causing reproductive toxicity" given in regulation (22 CCR 12306[g]) appear to have been satisfied for the chemicals in the table

below. In making this evaluation, OEHHA relied upon the documents and reports cited by US EPA in making their finding that the specified chemicals cause reproductive toxicity. In some cases, OEHHA consulted additional sources of information on the specific studies cited by US EPA. This was done only where necessary to affirm or clarify details of results and study design for studies cited by US EPA; OEHHA did not review additional studies not relied on by US EPA.

A major source of information used by the US EPA was the "Tox-Oneliner" database maintained by US EPA's Office of Pesticide Programs (OPP). This database consists of brief summaries of (usually unpublished) data submitted to the Agency in compliance with regulatory requirements. Many database entries include a notation of "core grade" – a system formerly used by US EPA to indicate the extent to which a study conformed to published test guidelines (US EPA 1983a and 1983b). Under this scheme, a "core grade guideline" study was considered to meet all guideline requirements; a "core grade minimum" study was considered sufficient for risk assessment; and a "core grade supplementary study" was considered to provide useful supplementary information, but not to be suitable for risk assessment on its own.

Studies cited by US EPA in making findings with regard to reproductive toxicity are briefly described below. The statements in bold reflect data and conclusions which appear to satisfy the criteria for sufficiency of evidence for reproductive toxicity in regulation (22 CCR 12306[g]). Where a notation of "not stated" has been made, OEHHA staff were unable to find an explicit statement of a particular detail such as the number of animals in each dose group. Where NOELs (no-observed-effect-level), LOELs (lowest-observed-effect-level), or LELs (lowest-effect-level) are included in the study descriptions below, they are quoted directly from the cited references.

Chemical	Chemical Abstracts No.	DART Endpoints	Pesticide status or usage
Cycloate	1134-23-2	Developmental toxicity	Registered in CA
Diclofop Methyl	51338-27-3	Developmental toxicity	Registered in CA
Fenoxaprop Ethyl	66441-23-4	Developmental toxicity	Registered in CA
Hydramethylnon (Amdro)	67485-29-4	Developmental toxicity, male reproductive toxicity	Registered in CA
Linuron	330-55-2	developmental toxicity	Registered in CA
Myclobutanil	88671-89-0	Developmental toxicity, male reproductive toxicity	Registered in CA
Propachlor	1918-16-7	Developmental toxicity	Pesticide, not currently registered in CA
Sodium nitrite	7632-00-0	Developmental toxicity	Meat preservative

Studies cited by US EPA in making findings with regard to reproductive toxicity are briefly described below. The statements in bold reflect data and conclusions which appear to satisfy the criteria for sufficiency of evidence for reproductive toxicity in regulation (22 CCR 12306[g]). Where a notation of "not stated" has been made, OEHHA staff were unable to find an explicit statement of a particular detail such as the number of animals in each dose group.

Cycloate (CAS No. 1134-23-2)

Developmental toxicity **has been manifested as decreased pup weight and survival in rat studies.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing cycloate on EPCRA section 313(d)(2)(B) based on the available . . . developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states:

> "Decreased weight and survival were observed in the offspring of rats orally administered 24 mg/kg/day (LOEL) and 72 mg/kg/day of cycloate, respectively (duration and frequency not reported). The reproductive NOEL was 8 mg/kg/day. Decreased pup weight was observed at 20 mg/kg/day and decreased pup survival was observed at 50 mg/kg/day in a 2-generation rat reproduction study. The NOEL values for these endpoints were 2.5 mg/kg/day and 20 mg/kg/day, respectively. Other studies which tested doses up to 400 mg/kg/day failed to find any reproductive or developmental effects."

Details of the studies cited by US EPA in support of the TRI listing were obtained from the California Department of Pesticide Regulations' Summary of Toxicology Data on Cycloate (CDPR, 1994). The CDPR (1994) and US EPA (1993a) report the same developmental NOEL and LOEL for each of the studies.

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR12306, and notes the following:

1. **Adequacy of the experimental design:**
   Both studies appear to be acceptable under FIFRA. US EPA (1993a) stated that the 2-generation rat reproduction study was rated "supplementary" because the test compound was not identified in the report.
2. **Route of administration:**
   Oral, in diet for both studies
3. **The frequency and duration of exposure:**
   Continuous, in diet
4. **The numbers of test animals:**
   Study a) 3-generation rat reproduction study: 15 males, 30 females per generation,
   Study b) 2-generation rat reproduction study: 25 per sex per group
5. **The choice of species:**
   The rat is a standard test species

6. **The choice of dosage levels:**
   Study a) 3-generation rat reproduction study: 0, 8, 24, 72 mg/kg/day,
   Study b) 2-generation rat reproduction study: 0, 50, 400, 1000 ppm (approximately equivalent to 0, 2.5, 20, 50 mg/kg/day).
7. **Maternal toxicity:**
   In both reproduction studies, parental and developmental toxicity occurred at the same doses. For both rat reproduction studies, parental toxicity consisted of decreased body weight at the 2 highest doses (CDPR, 1994). In addition, F0 and F1 breeding adults in the 2-generation study had mineralization of the brain and biliary hyperplasia at the highest dose, and thoracic and sacral spinal cord degeneration at the two highest doses (females only). In the TRI final rule document (US EPA, 1994a), the Agency states with specific reference to cycloate: "As described in unit IV.E. of this preamble, developmental effects seen in developing organisms are considered to be adverse whether or not they occur at doses that are also maternally toxic."

Diclofop Methyl (CAS No. 51338-27-3)

Developmental toxicity **has been manifested as increased resorptions and pup mortality, reduced body weights, and effects on the kidneys.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing diclofop methyl on EPCRA section 313(d)(2)(B) based on the available developmental . . . toxicity data."

Supporting documentation for the TRI listing (US EPA, 1993a) states, "In a rat teratology study, increased resorptions, reduced body weights, and dilation of the renal pelvis or distention of the ureter in offspring were reported in rats fed 1.6 mg/kg/day (LOEL). The NOEL was 0.5 mg/kg/day. Increased pup mortality was observed at 5 mg/kg/day (LOEL) in a 3-generation rat reproduction study. The NOEL was 1.5 mg/kg/day."

The TRI listing is based on the description of the two primary studies by the US EPA (1993d) Tox-One-Liner for diclofop methyl. The 1986 Summary of Toxicology Data for Diclofop-Methyl by the California Department of Food and Agriculture summarizes the same studies.

The US EPA Final Rule (1994b) reaffirmed that there is sufficient evidence for listing diclofop-methyl based on the available developmental . . . toxicity data. The Final Rule also noted that in the rat teratology study, the Agency erred in interpreting gavage doses as diet concentrations (ppm) in the TRI listing (US EPA, 1993b). The actual doses for the developmental NOEL and LOEL are 10 and 32 mg/kg/day, respectively.

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Both studies were rated as Core Grade Minimum.
2. **Route of administration:**
   Study a) rat teratology study - oral gavage,
   Study b) 3-generation rat reproduction study - oral, in diet
3. **The frequency and duration of exposure:**
   Study a) rat teratology study - each of gestation days 6-15,
   Study b) 3-generation rat reproduction study - continuous, in diet
4. **The numbers of test animals:**
   Study a) rat teratology study - 20 per group,
   Study b) 3-generation rat reproduction study - 10 males and 15 females per group; 3 generations, 2 litters per generation
5. **The choice of species:**
   The rat is a standard test species.
6. **The choice of dosage levels:**
   Study a) rat teratology study - 0, 10, 32, 100 mg/kg/day,
   Study b) 3-generation rat reproduction study - 0, 10, 30, 100 ppm (equivalent to 0, 0.5, 1.5, 5 mg/kg/day).
7. **Maternal toxicity:**
   Study a) rat teratology study - the maternal LOEL of 10 mg/kg/day (lowest dose tested) is based on increased liver weights,
   Study b) 3-generation rat reproduction study - no maternal toxicity apparent.

Fenoxaprop Ethyl (CAS No. 66441-23-4)

Developmental toxicity **has been manifested as decreased viability, impaired growth and delayed ossification.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing fenoxaprop ethyl on EPCRA section 313(d)(2)(B) based on the available . . . developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states:

> "In a developmental toxicity study, fetotoxic effects (slightly impaired growth and delayed ossification) were reported at 100 mg/kg/day. The NOEL was 32 mg/kg/day. These effects were observed at doses that were also toxic to maternal animals. In a two-generation reproductive toxicity feeding study in rats, decreased survival, decreased body weight at study termination, and significant changes in kidney and liver weights were reported in the F2a and F2b litters. The fetotoxic

> LOEL in this study was 5 ppm (0.25 mg/kg/day, the lowest dose tested). The LOEL and NOEL for maternal toxicity (increased kidney and liver weights) were 80 ppm [180 ppm, see below] (4 mg/kg/day) and 30 ppm (1.5 mg/kg/day), respectively. Thus, the fetotoxic effects were observed at doses lower than those that produced maternal toxicity."

The TRI listing is based on the evaluation of the two primary studies by US EPA (1993a) in its Tox One-Liner Database for fenoxaprop ethyl. However, a discrepancy was observed in the Tox One-Liner obtained by OEHHA (US EPA, 1989) concerning the highest dose tested in the two-generation rat study. The Tox One-Liner (US EPA, 1989) lists the highest dose as 180 ppm and the maternal LEL (highest dose tested) as 80 ppm. The difference appears to be due to a typographical error in the Tox One-Liner, listing the maternal LEL as 80 ppm rather than the true dose of 180 ppm, that was carried over into the TRI document (US EPA, 1993a). Correction of this error would result in a change of the LEL, but not the NOEL, for maternal toxicity.

For the rat teratology study, US EPA (1989) noted that the doses tested were 0, 10, 32, 100 mg/kg by gavage in Wistar rats. The fetotoxic NOEL and LEL were 32 and 100 mg/kg, respectively, based on slightly impaired growth and delayed ossification. The maternal NOEL and LEL were also 32 and 100 mg/kg, respectively, based on reduced body weight gain.

In the two-generation rat reproduction study, US EPA (1989) noted that the dose levels tested were 0, 5, 30, and 180 ppm. The fetotoxic NOEL was < 5 ppm (lowest dose tested), based on decreased survival and terminal body weights and significant changes in kidney and liver weights for F2a and F2b generations. The maternal NOEL and LEL were 30 and [180] ppm, respectively, based on increased liver and kidney weight.

US EPA (1989) lists a "replacement" two-generation rat reproduction study that has the same dose levels, but different toxic endpoints than the two-generation rat reproduction study listed in the TRI document (US EPA, 1993a). The "replacement" study lists an offspring NOEL and LEL of 5 and 30 ppm, based on decreased body weight at day 21 post-partum. The 5 ppm NOEL was most recently restated by US EPA (1991a) and was considered as support of the tolerances for fenoxaprop ethyl.

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Both studies are listed as Core Grade Minimum.
2. **Route of administration:**
   Study a) rat teratology study - oral gavage,
   Study b) 2-generation rat reproduction study - oral, in diet.
3. **The frequency and duration of exposure:**

Study a) rat teratology study - not stated directly, but the study was considered to meet guideline specifications which require treatment daily on gestation days 6-15,

Study b) 2-generation rat reproduction study - not stated, but guideline requirements specify treatment continuously from before mating of parental generation; throughout mating, gestation and lactation; and continued into the 2d generation.

4. **The numbers of test animals:**
   Not stated directly for either study, but guidelines specify a minimum of 20 pregnant rats per dose group.
5. **The choice of species:**
   The rat is a standard test species.
6. **The choice of dosage levels:**
   Study a) rat teratology study - 0, 10, 32, 100 mg/kg/day,
   Study b) 2-generation rat reproduction study - 0, 5, 30, 180 ppm (equivalent to approximately 0, 0.25, 1.5, 9 mg/kg/day).
7. **Maternal toxicity:**
   Study a) rat teratology study - maternal and developmental toxicity occurred at the same doses (NOEL 32 mg/kg/day; LEL 100 mg/kg/day),
   Study b) 2-generation rat reproduction study - Fetotoxic effects (5 ppm) were observed at doses lower than those that produced maternal toxicity (NOEL 30 ppm; LEL 180 ppm).

Hydramethylnon (CAS No. 67485-29-4)

Developmental toxicity **has been manifested as decreased fetal body weights, increased post-implantation loss and vertebral abnormalities.** ***Male reproductive toxicity*** **has been manifested as testicular atrophy and infertility.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing hydramethylnon on EPCRA section 313(d)(2)(B) based on the available reproductive, [and] developmental . . . toxicity data for this chemical."

For reproductive toxicity, supporting documentation for the TRI listing (US EPA, 1993a) states, "In a 90-day dog feeding study, testicular atrophy was observed at 6 mg/kg/day (LOEL). The NOEL was 3 mg/kg/day. In a 90-day rat study, dietary administration of 5 mg/kg/day (LOEL) produced testicular atrophy. The NOEL was 2.5 mg/kg/day. Dietary administration of 6.5 mg/kg/day for 18 months produced testicular lesions in mice. The NOEL was 2.75 mg/kg/day. In a 2-year rat study, dietary administration of 5 mg/kg/day produced decreased testicular weight and testicular atrophy. The NOEL was 2.5 mg/kg/day. In a 3-generation rat reproduction study, oral administration of 5 mg/kg/day produced male infertility. The NOEL was 2.5 mg/kg/day." For developmental toxicity, supporting documentation for the TRI listing (US EPA, 1993a) states, "Decreased fetal

weight was observed in the offspring of rats administered 30 mg/kg/day (LOEL). The NOEL was 10 mg/kg/day. Increased post-implantation loss and decreased fetal viability were observed in the offspring of rabbits administered 15 mg/kg/day (LOEL). The NOEL was 5 mg/kg/day. Vertebral anomalies were seen in the offspring of rabbits administered 10 mg/kg/day (LOEL). The NOEL was 5 mg/kg/day."

The TRI listing is based on evaluations of 7 studies summarized in IRIS (US EPA, 1993c) and in the US EPA Tox One-Liner for hydramethylnon (US EPA, 1993d). In lieu of being able to obtain the US EPA one-liner for the chemical, IRIS (US EPA, 1992) and the California Department of Pesticide Regulation's Summary of Toxicology Data on Hydramethylnon (CDPR, 1993) were referred to for their largely complete summaries of all studies supporting the TRI listing.

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   All 7 studies were rated Core Grade Minimum
2. **Route of administration:**
   Study a) 90-day dog feeding study - oral, in gelatin capsules
   Study b) 90-day rat feeding study - oral
   Study c) 18-month mouse feeding study - oral, in diet
   Study d) 2-year rat feeding study - oral, in diet
   Study e) 3-generation rat reproduction study - oral, in diet
   Study f) rat teratology study - oral gavage
   Study g) rabbit teratology study - oral gavage
3. **The frequency and duration of exposure:**
   Study a) 90-day dog feeding study - dosed once per day
   Study b) 90-day rat feeding study - unspecified, probably continuous in diet for 90 days
   Study c) 18-month mouse feeding study - continuous, in diet
   Study d) 2-year rat feeding study - continuous, in diet
   Study e) 3-generation rat reproduction study - continuous, in diet. The two highest dose groups were discontinued after F0 generation parents had been evaluated in a recovery experiment.
   Study f) rat teratology study - each of gestation days 6-15
   Study g) rabbit teratology study - each of gestation days 6-18
4. **The numbers of test animals:**
   Study a) 90-day dog feeding study - unspecified
   Study b) 90-day rat feeding study - unspecified
   Study c) 18-month mouse feeding study - unspecified
   Study d) 2-year rat feeding study - 50 per sex per dose
   Study e) 3-generation rat reproduction study - 12 males and 24 females per treatment group

Study f) rat teratology study - 26 per group
Study g) rabbit teratology study - 16 per group

5. **The choice of species:**
   Rats, rabbits, mice and dogs are standard test species
6. **The choice of dosage levels:**
   Study a) 90-day dog feeding study - 0, 3, 6, 12 mg/kg/day
   Study b) 90-day rat feeding study - total dose levels unspecified, at least 0, 50, 100 ppm (equivalent to 0, 2.5, 5 mg/kg/day).
   Study c) 18-month mouse feeding study - 0, 25, 50, 100, 200 ppm (equivalent to 0, 2.75, 3.75 mg/kg/day, for control group and two lowest treatment groups, respectively. Equivalent mg/kg/day at two highest doses is not known),
   Study d) 2-year rat feeding study - 0, 25, 50, 100, 200 ppm (equivalent to 0, 1.25, 2.5, 5, 10 mg/kg/day),
   Study e) 3-generation rat reproduction study - 0, 25, 50, 100, 200 ppm (equivalent to 0, 1.25, 2.5, 5, 10 mg/kg/day),
   Study f) rat teratology study - 0, 3, 10, 30 mg/kg/day,
   Study g) rabbit teratology study - 0, 5, 10, 20 mg/kg/day.
7. **Maternal toxicity:**
   Study a) not applicable
   Study d) not applicable
   Study e) 3-generation rat reproduction study - Maternal and reproductive toxicity occurred at the same doses. The maternal NOEL and LEL were 50 and 100 ppm, respectively, based on decreased food consumption and body weight gain,
   Study f) rat teratology study - maternal toxicity occurred at a dose below that which caused developmental toxicity. The maternal NOEL and LEL were 3 and 10 mg/kg/day, respectively, based on decreased mean body weight gain and discoloration of body fat,
   Study g) rabbit teratology study - maternal toxicity occurred at a dose below that which caused developmental toxicity. The maternal LEL (lowest dose tested) was 5 mg/kg/day, respectively, based on decreased body weight gain. It should be noted that gestational weight gain in rabbits is known to be highly variable, and is therefore not generally considered an accurate indication of maternal toxicity (US EPA, 1991b).

Linuron (330-55-2)

Developmental toxicity **has been manifested as decreased fetal body weights and viability, and an increase in skull malformations.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing linuron on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available hematological and developmental toxicity data for this chemical." Supporting documentation for this listing (US EPA, 1993c) states, "In a separate teratogenicity feeding study in rats, a LOAEL of 31.25 mg/kg/day was based on an increased incidence of resorptions; the LOAEL for maternal toxicity in this study was 6.25 mg/kg/day (NOEL 2.50 mg/kg/day) based on decreased food consumption and decreased body weight gain. An oral teratology study in rabbits indicated a LOAEL of 5 mg/kg/day (lowest dose tested) based on decreased fetal body weight, decreased litter size and an increase in skull malformations (IRIS, 1993)."

The *Reregistration Eligibility Decision* document (RED; US EPA, 1995) discusses the same two developmental toxicity studies. In both IRIS and the RED document, the same adverse effects on development are reported. However, for both studies, there are differences between the two US EPA documents in the doses reported as effective.

> For the rat study, the RED document states, "The NOELs for maternal systemic toxicity and developmental toxicity were 125 ppm (12.1 mg/kg/day). The LOEL of 625 ppm (49.8 mg/kg/day) for maternal systemic toxic effects was based upon decreased body weight and food consumption values. The developmental toxicity LOEL of 625 ppm (49.8 mg/kg/day) was based on increased in postimplantation loss and increases in the litter and fetal incidences of resorptions."
>
> For the rabbit study, the RED document states, ". . . a maternal systemic toxicity LOEL was observed at the 25 mg/kg/day level, based upon reduced maternal body weight, thereby defining the NOEL as 5 mg/kg/day. At the high-dose level (100 mg/kg/day) maternal body weight, food consumption, absolute liver weight, and liver-to-body weight ratios were decreased. The developmental toxicity NOEL was determined to be 25 mg/kg/day, based upon an increased number of abortions, decreased mean number of fetuses per litter, decreased fetal body weight, and increased incidence of fetuses with skeletal variations of the skull at the 100 mg/kg/day level (the developmental toxicity LOEL)."

Based on the results of these studies, US EPA (1995) concluded, "Due to the short-term and intermediate-term endpoints based on maternal and developmental concerns, the Agency is requiring minimum handler personal protective equipment requirements for any end-use product containing linuron."

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA Toxic Release Inventory list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat developmental toxicity study - the US EPA (1995) *RED* document states that this study satisfies guideline requirements.
   Study b) rabbit developmental toxicity study - the US EPA (1995) *RED* document states that this study satisfies guideline requirements.
2. **Route of Administration** - Oral
3. **The frequency and duration of exposure:**
   Study a) rat developmental toxicity study - each of gestation days 6 -15.
   Study b) rabbit developmental toxicity study - each of gestation days 7 through 19.
4. **The numbers of test animals:** Not stated for either study. However, guidelines require a minimum of 20 rats or 12 rabbits per dose group.
5. **The choice of species:** The rat and rabbit are standard test species.
6. **The choice of dosage levels:**
   Study a) rat developmental toxicity study - 0, 5.0, 12.1, 49.8 mg/kg/day,
   Study b) rabbit developmental toxicity study - 0, 5, 25, 100 mg/kg/day
7. **Maternal toxicity:** In both studies, it cannot be concluded that developmental toxicity is secondary to maternal toxicity. In the rabbit study, the evidence for maternal toxicity was primarily reduced maternal body weights. It should be noted that gestational weight gain in rabbits is known to be highly variable, and is therefore not generally considered an accurate indication of maternal toxicity. More generally, US EPA *Guidelines for Developmental Toxicity Risk Assessment* (US EPA, 1991b) state, "Current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity; rather when the LOAEL is the same for adult and developing organisms, it may simply indicate that both are sensitive to that dose level."

Myclobutanil (CAS No. 88671-89-0)

Male reproductive toxicity **has been manifested as testicular atrophy and abnormal histopathology of the seminiferous tubules.** ***Developmental toxicity*** **has been manifested as reduced viability.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing myclobutanil on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available . . . reproductive and developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states that, "Testicular atrophy (the LOEL was 9.84 mg/kg/day, the NOEL was 2.49 mg/kg/day) was observed in a 2-year chronic feeding study in rats (11 [US EPA 1993c]). The seminiferous tubules

were frequently devoid of spermatid formation and germinal epithelial cells. . . Testicular atrophy (the LEL was 46.4 mg/kg/day, the NOEL was 9.28 mg/kg/day) was also noted in a 2-generation reproduction study (Core Guideline) (11 [US EPA 1993c])." The TRI supporting documentation also discusses developmental toxicity studies in rats and rabbits: "In a developmental toxicity study in rats, increased resorption and decreased viability were observed at 93.8 mg/kg/day (LOEL). The NOEL was 31.3 mg/kg/day (24 [US EPA, 1993d]). In a developmental toxicity study in rabbits, an increased number of resorptions per litter, reduced viability index, and reduced litter size were observed at 200 mg/kg/day (LOEL). The NOEL was 60 mg/kg/day."

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) 2-year chronic feeding study in rats - used as critical study for oral RfD, study is stated to be of good quality and was given a high confidence rating.
   Study b) 2-generation reproductive toxicity study in rats - rated as core-grade guideline.
   Study c) developmental toxicity study in rats - rated as core-grade minimum.
   Study d) developmental toxicity study in rabbits - study rated as core-grade minimum.
2. **Route of administration:**
   Oral for all 4 studies
3. **The frequency and duration of exposure:**
   Study a) daily for 24 months,
   Study b) not stated, but guidelines specify daily prior to mating and throughout mating, gestation, and lactation for the parental generation; and continuously for subsequent generations until the end of the study,
   Study c) treatment on each of gestation days 6 - 15,
   Study d) not stated, but guidelines specify treatment on each of gestation days 6 - 18.
4. **The numbers of test animals:**
   Study a) 27-28 animals of each sex per dose group,
   Study b) not stated, but guidelines specify a minimum of 20 males per dose group, and sufficient females to ensure a minimum of 20 pregnant at or near term,
   Study c) not stated, but guidelines specify a minimum of 20 animals per dose group,
   Study d) not stated, but guidelines specify a minimum of 12 animals per dose group.
5. **The choice of species:**
   Rats and rabbits are standard test species for toxicity studies.
6. **The choice of dosage levels:**

Study a) The overall mean daily consumption for males was 0, 2.49, 9.84, or 39.21 mg/kg bw/day.
Study b) 0, 2.32, 9.28, 46.4 mg/kg bw/day.
Study c) 0, 31.26, 93.77, 312.58, and 468.9 mg/kg/day.
Study d) 0, 20, 60, and 200 mg/kg/day.

7. **Maternal toxicity:**
   Study a & b) not relevant
   Study c) maternal: NOEL 312.6 mg/kg/day, LEL 468.9 mg/kg/day; developmental: NOEL 31.3 mg/kg/day, LEL 93.8 mg/kg/day.
   Study d) maternal: NOEL 20 mg/kg/day, LEL 60 mg/kg/day; developmental: NOEL 60 mg/kg/day, LEL 200 mg/kg/day.

Propachlor (CAS No. 1918-16-7)

Developmental toxicity **was manifested as decreased fetal viability.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . .there is sufficient evidence for listing Propachlor on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data."

Supporting documentation for the TRI listing (US EPA, 1993a) states that, "No evidence of maternal toxicity was seen in rabbits administered propachlor by gavage at 0, 5, 15, or 50 mg/kg/day on days 7- 19 of gestation (11 [US EPA, 1993c]). Statistically significant increases in mean implantation loss with corresponding decreases in the mean number of viable fetuses were reported at 15 and 50 mg/kg/day when compared to controls." An additional oral study, performed in rats, found no evidence of maternal or developmental toxicity. The TRI supporting documentation also cites a 10-day health advisory for propachlor, which is based upon the rabbit developmental toxicity data (US EPA, 1988).

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) Rabbit: details of study design appear to meet FIFRA test guideline requirements,
   Study b) Rat: stated to meet US EPA core-grade minimum requirements.
2. **Route of administration:**
   Oral for both studies
3. **The frequency and duration of exposure:**
   Study a) Rabbit: daily on gestation days 7-19,
   Study b) Rats: not stated, but as the study was stated to meet FIFRA requirements, exposure would have been daily on each of gestation days 6-15 in rats.

4. **The numbers of test animals:**
   Study a) Rabbit: 16 animals per dose group,
   Study b) Rat: not stated, but as the study was stated to meet FIFRA requirements, would have been a minimum of 20 animals per dose groups.
5. **The choice of species:**
   Rabbits and rats are standard test species for toxicity studies.
6. **The choice of dosage levels:**
   Study a) Rabbit: 0, 5, 15, 50 mg/kg/day,
   Study b) Rat: 0, 20, 60, or 200 mg/kg/day.
7. **Maternal toxicity:**
   Study a) Rabbit: It is specifically stated that developmental toxicity was observed at doses lower than those causing maternal toxicity,
   Study b) It is specifically stated that no maternal or developmental toxicity was observed.

Sodium nitrite (CAS No. 7632-00-0)

Developmental toxicity **has been manifested as reduced viability and adverse effects on growth, including biochemical and/or metabolic changes.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing sodium nitrite on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available . . . developmental toxicity data for this chemical."

The US Environmental Protection Agency (US EPA, 1994a) stated that,

> "Fetotoxicity (fetal death) was reported following oral exposures of pregnant rats to sodium nitrite (30 mg/kg/day) during gestation days 1 through 22. In mice, exposed orally to 80 mg/kg/day during gestation days 6 to 15 there was increased preimplantation loss and fetal death, and in mice exposed to a lower dose (20 mg/kg/day) during gestation days 1 to 14, abnormalities of the blood or lymphatic system were reported in offspring. In offspring of rats orally exposed to 26 to 256 mg/kg/day during pregnancy (gestation days 1 through 22) and/or lactation (20 to 21 days after birth), effects on growth including biochemical and/or metabolic changes were noted".

Information such as species and number of animals used; doses, route, and days of treatment; and details of toxicological findings was provided, or obtained from the original studies cited (Globus and Samuel, 1978; Roth *et al.,* 1987; Shuval and Gruener, 1972) .

It was also noted in the US EPA proposed rule document (US EPA, 1994a) that sodium nitrite causes methemoglobinemia. Newborn infants are known to be particularly susceptible to this effect, in part because of the continued presence of fetal hemoglobins

in their erythrocytes. The rate of nitrate-induced oxidation of fetal hemoglobin to methemoglobin is approximately twice that found for adult hemoglobin. As fetuses are dependent on fetal hemoglobins to carry oxygen to their tissues, it is expected that fetuses would also be particularly sensitive to any sodium nitrate reaching their bloodstream.

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   All of the studies, with the exception of a Japanese developmental study in mice exposed to sodium nitrite on gestational days 6-15, were reviewed in the original publications. All of the studies reviewed appeared to be adequately designed and conducted.
2. **Route of Administration**
   Oral
3. **The frequency and duration of exposure:**
   Rat gestation days 1-22; rat gestation days 1-22 and lactation days 1-20; mouse gestation days 1-14, mouse gestation days 6-15
4. **The numbers of test animals:**
   Rat gd 1-22 (7-12 animals/group); rat gd 1-22 and ld 1-20 (5-8 animals/group); mouse gd 1-14 (4, 9, 12 or 23 animals/group); mouse gd 6-15 (not known).
5. **The choice of species:**
   The rat and mouse are standard test species.
6. **The choice of dosage levels:**
   30 mg/kg/d; 26-256 mg/kg/d; 20 mg/kg/d; 80 mg/kg/d
7. **Maternal toxicity:**
   Minimal maternal toxicity (reduced fluid intake and weight gain in late gestation) was reported in one rat study. No parameters related to possible maternal toxicity were reported in the other studies reviewed.

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